59 Conclude polyoxypropylene glycol molecule whereby the solution is aqueous at 1 to 30°C and gelatinizes at about 37°C.

Cancel claim 13.

REMARKS

Reconsideration of this application is requested in view of the amendments to the Specification and Claims and the remarks presented herein.

The claims in the application are claims 2 to 5, 8 to 11, 14 and 15, all other claims having been cancelled. Claim 13, which the Examiner said was improperly dependent, was cancelled in the amendment of June 29, 2001. Since the June 29, 2001 amendment was not entered, claim 13 has been cancelled herein. Also, it is noted that in the Advisory Action, claims 10 and 11 were omitted from the pending claims. Claims 10 and 11 have never been cancelled.

The specification has been amended to use the correct nomenclature found in original claim 2.

With respect to the Examiner's request that the sequence ID number be used in claims 4, 5 and 11, Applicants do not understand the Examiner's sudden request for insertion of SEQ ID No: 1 into the claims since this is only one particular form of the protein

MP52 one of which contains only 119 amino acids. MP52 can contain 1 or 2 additional amino acids at the N-terminus and, therefore, Applicants do not wish to limit the claims to the MP52. It can be clearly seen from the Japanese application, which was originally referred to in the application and is now referred to by its U.S. serial number, MP52 is the normal mature protein. Therefore, the claims as amended are believed to be drawn to patentable subject matter for the reasons set forth in the amendment filed on September 11, 2001.

Also, there are several publications concerning MP52 and BMPZ. These proteins are known and are not deemed "new" for purposes of patenting in this application. For example, see U.S. Patent Nos. 5,994,094, 5,756,457 and WO 95/07108. Copies of the pertinent portions of the '457 and '108 references are attached.

The Examiner requested that a unit indication for molecular weight be indicated in claim 14. In specialized literature on "pluronics" the molecular weight is mentioned in the form of a number without unit indication. A molecular weight is defined as the weight of a molecule resulting from the sum of the weight of all atoms having the unit dalton. If no unit indication is made, it is assumed that dalton is meant. Thus, it is not necessary to

include it in the claim. Therefore, favorable reconsideration of the application is requested.

Respectfully submitted,
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CAM:sd
Enclosures: Amended Fig. 1
Pertinent portions of U.S. Patent No. 5,756,457 and WO 95/07108
Marked-Up Version of Specification and Claims
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

Paragraph beginning at page 1, line 6 has been amended as follows:

The present invention relates to a cartilage and bone morphogenetic repairing [material] composition for the treatment of bone fracture and bone defect. In more detail, this invention is concerned with the cartilage and bone morphogenetic repairing [material] composition which contains a polyoxyethylene-polyoxypropylene glycol and a bone morphogenetic protein.

Paragraph beginning at page 4, line 16 has been amended as follows:

This invention is concerned with a cartilage and bone morphogenetic repairing [material] composition which contains a polyoxyethylene-polyoxypropylene glycol and a bone morphogenetic protein.

Paragraph beginning at page 6, line 29 to page 7, line 14 has been amended as follows:

Moreover, this invention relates to a cartilage and bone morphogenetic repairing [material] composition wherein a concentration of polyoxyethylene-polyoxypropylene glycols as described above in an aqueous solution is about 10-50%. It is known that the reversible phase transition temperature of

polyoxyethylene-polyoxypropylene glycols varies in general depending on the concentration of their prepared aqueous solutions, and the polyoxyethylene-polyoxypropylene glycols within the above-mentioned constituent ranges may gelate at around body temperature, i.e. about 37°C at a concentration of about 10-90% in its aqueous solution. As the most preferable example, there is prepared the polyoxyethylene-polyoxypropylene glycol block polymer aqueous solution of 15-30% concentration having a molecular weight of polypropylene glycol of 3,850 and a ethylene oxide content of 70% (Pluronic F-127).

Paragraph beginning at page 7, line 19 to page 8, line 9 has been amended as follows:

The bone morphogenetic proteins used in this invention include, but are not limited to, a series of proteins belonging to the TGF-β gene superfamily such as BMP-2 to BMP-9 and so on, the protein named MP52, the protein named GDF-5 and the like. Particularly preferable BMP-2 is a protein produced using Chinese hamster ovary (CHO) cells according to the genetic engineering technology reported by Wang, et al. (Proc. Natl. Acad. Sci. USA 87, 2220-2224, 1990 and U.S. Patent No. 4,877,864), and particularly preferable MP52 is a new protein produced according to the genetic engineering technology suggested by the present inventors (our copending Japanese Patent Application [No. 93644/1995).] Serial No. 531,621 filed October 20, 1977). This new

protein can be produced by constructing a plasmid containing the DNA sequence coding the amino acid sequence as shown in SEQ ID No.:1 of the Sequence Listing derived from MP52 and having added the codon coding methionine at the N-terminal of said DNA sequence; transforming the plasmid into E. coli; incubating the E. coli to obtain an inclusion body; and solubilizing and purifying the inclusion body to obtain a monomer protein, which is then dimerized and purified.

Paragraph beginning at page 9, line 17 has been amended as follows:

[Fig. 3 is] Figs 3a and 3b are microscopic photographs of the stained tissues of the non-decalcified sections of the femur of the right hind leg of the mouse as obtained by Example 4. Formations of bone matrices and bone matrices together with osteoblasts and of bone marrows can be confirmed by von-Kossa staining (a) and Hexatoxylin-Eosin staining (b), respectively.

Paragraph beginning at page 19, line 30 to page 20, line 7 has been amended as follows:

The cartilage and bone morphogenetic repairing [material] composition according to the invention can be applied to the affected site in the bone fracture therapy requiring no surgical operation in a simple and painless manner due to a high bio-absorption, a favorable affinity to the active ingredient, i.e., a

bone morphogenetic protein, and a temperature dependent sol-gel reversible transition. Thus, the drug effect of a bone morphogenetic protein may be sustained and further a cartilage and bone morphogenetic repairing composition with less side-effects may be provided.

The cartilage and bone morphogenetic repairing composition as claimed in claim 14, wherein the polypropylene glycol as a constituent of said polyoxyethylene-polyoxypropylene glycol has a molecular weight of about 1,500-4,000 and the ethylene oxide content is about 40-80% per molecule.

IN THE CLAIMS:

Claim 13 has been cancelled.

Claim 2 has been amended as follows:

2. (Twice amended) The cartilage and bone morphogenetic repairing [material] composition as claimed in claim 14, wherein the polypropylene glycol as a constituent of said polyoxyethylene-polyoxypropylene glycol has a molecular weight of about 1,500-4,000 and the ethylene oxide content [of] is about 40-80% per molecule.

Claim 8 has been amended as follows:

8. (Amended) The method of claim [7] 15 wherein the polypropylene glycol as a constituent of the polyoxyethylene-polyoxypropylene glycol of said composition has a molecular weight of about 1,500 to 4,000 and [an] the ethyleneoxide content of the polyoxyethylene-polyoxypropylene glycol is about 40 to 80% per molecule.

Claim 9 has been amended as follows:

9. (Amended) The method of claim 8 wherein the polyoxyethylene-polyoxypropylene glycol is about 10 to 50% by weight of [an] the aqueous solution.

Claim 14 has been amended as follows:

14. (Thrice amended) A cartilage and bone morphogenetic repairing composition comprising a collagen-free aqueous solution of a polyoxyethylene-polyoxypropylene glycol and an effective amount of a bone morphogenetic protein, the molecular weight of polypropylene glycol as a constituent of said polyoxyethylene-polyoxypropylene glycol molecule is 900 to 4000 and the ethylene oxide content is 5 to [95%] 90% by weight of the polyoxyethylene-polyoxypropylene glycol molecule whereby the solution is aqueous at 1 to 30°C and gelatinizes at about 37°C.